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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
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(54) Title: OLANZAPINE PAMOATE DIHYDRATE

(57) Abstract: The present invention relates olanzapine pamoate dihydrate, pharmaceutical compositions thereof and use in treating certain mental disorders, such as schizophrenia. X-16133

OLANZAPINE PAMOATE DIHYDRATE

BACKGROUND OF THE INVENTION

Olanzapine has shown great promise in the treatment of patients suffering
5 from schizophrenia and is currently being marketed for that purpose. However, such
patients are often non-compliant, making it difficult to assess whether or not a patient has
received the proper dosage of medication. It is therefore desirable to formulate
olanzapine in a sustained release or depot formulation to assure consistent and proper
dosage of the drug substance and to assure compliance. United States Patent No.
10 6,169,084 B1 discloses certain olanzapine pamoate salts and solvates thereof, such as the
olanzapine pamoate monohydrate, which are useful in preparing such sustained release or
depot formulations.

In order to achieve a sustained release formulation of 2 to 4 weeks, for example,
an injectable, slow to dissolve form of the active compound is needed. Surprisingly,
15 olanzapine pamoate can be prepared in the dihydrate form. In addition, olanzapine
pamoate dihydrate is substantially less soluble in aqueous solution than olanzapine
pamoate monohydrate. Thus, the olanzapine pamoate dihydrate has excellent properties
for use as a depot preparation.

SUMMARY OF THE INVENTION

20 The present invention provides a compound which is olanzapine pamoate
dihydrate.

The present invention further provides a pharmaceutical composition comprising
olanzapine pamoate dihydrate and a pharmaceutically acceptable carrier, diluent, or
25 excipient.

In addition, the present invention provides olanzapine pamoate dihydrate which is
substantially pure.

The present invention also provides a method of treating schizophrenia, acute
30 mixed or manic episodes associated with bipolar I disorder, agitation associated with
schizophrenia, agitation associated with bipolar I disorder, agitation associated with

dementia, or borderline personality disorder, comprising administering to a patient an effective amount of olanzapine pamoate dihydrate.

DETAILED DESCRIPTION OF THE INVENTION

5

XRPD Analysis

The X-ray powder diffraction (XRPD) pattern is obtained on a Siemens D5000 X-ray powder diffractometer, equipped with a $\text{CuK}\alpha$ source ($\lambda = 1.54056 \text{ \AA}$) and a Kevex solid state Si(Li) detector, operating at 50 kV and 40 mA. Each sample is scanned
10 between 4° and 40° in 2θ , with a step size of 0.02° in 2θ and a scan rate of 3.0 seconds/step, and with 1 mm divergence and receiving slits and a 0.1 mm detector slit. The dry powder is packed into recessed top-loading sample holders and a smooth surface is obtained using a glass slide.

The dihydrate may be identified by the presence of peaks at 8.1 ± 0.1 , 9.8 ± 0.1 ,
15 13.6 ± 0.1 , 16.3 ± 0.1 , 21.6 ± 0.1 , and $22.1 \pm 0.1^\circ$ in 2θ ; when the pattern is obtained from a copper radiation source ($\lambda = 1.54056$) at ambient temperature and 20-25% relative humidity. Peaks at 9.5 ± 0.1 , 16.0 ± 0.1 and $20.2 \pm 0.1^\circ$ in 2θ are also highly indicative of the presence of the dihydrate. It is understood by one of ordinary skill in the art that while relative peak intensities may vary due to changes in crystal habit, the characteristic peak
20 positions of the polymorph remain unchanged.

The angular peak positions in 2θ and corresponding I/I_0 data for all dihydrate peaks with intensities equal to or greater than 10% of the largest peak are tabulated in Table 2. All data in Table 2 is expressed with an accuracy of $\pm 0.1^\circ$ in 2θ .

Table 2. Angular Peak Positions in 2θ for Olanzapine Pamoate Dihydrate.

Angle ($^{\circ} 2\theta$)	I/I _o (%)
6.4	14.0
8.1	90.6
9.5	33.5
9.8	64.8
10.8	18.2
11.6	10.5
12.7	11.3
13.1	24.4
13.6	60.3
14.4	11.7
15.3	21.1
15.7	14.0
16.0	39.8
16.3	100.0
18.2	11.2
18.5	11.5
19.0	20.2
20.0	16.5
20.2	41.5
20.5	11.2
21.6	68.0
22.1	57.6
22.4	13.2
22.7	11.7
23.3	19.9
23.5	17.8
24.8	16.1
25.3	10.2

5 Solid State NMR

¹³C Cross polarization / magic angle spinning (CP/MAS) NMR (solid-state NMR or SSNMR) spectra is obtained using a Varian Unity Inova 400 MHz NMR spectrometer operating at a carbon frequency of 100.573 MHz and equipped with a complete solids accessory and a Chemagnetics 4.0 mm T3 probe. Ramped-amplitude cross polarization
10 (RAMP-CP) at 62 kHz and TPPM decoupling at 62-70 kHz are used. Acquisition parameters are as follows: 90° proton r.f. pulse width 4.0 μ s, contact time 1.0 ms, pulse

repetition time 10 s, MAS frequency 10.0 kHz, spectral width 50 kHz, and acquisition time 50 ms. Chemical shifts are referenced to the methyl group of hexamethylbenzene ($\delta = 17.3$ ppm) by sample replacement.

The dihydrate is analyzed via solid-state ^{13}C nuclear magnetic resonance (NMR) spectroscopy. Solid state ^{13}C chemical shifts reflect the molecular structure and electronic environment of the molecule in the crystal. The spectrum for the dihydrate comprises isotropic peaks at the following chemical shifts: 15.5, 43.6, 121.5, 123.2, 124.6, 127.3, 128.3, 130.3, 136.6, 148.8, and 162.4 ppm.

More specifically, the olanzapine pamoate dihydrate can be characterized by at least one of the following:

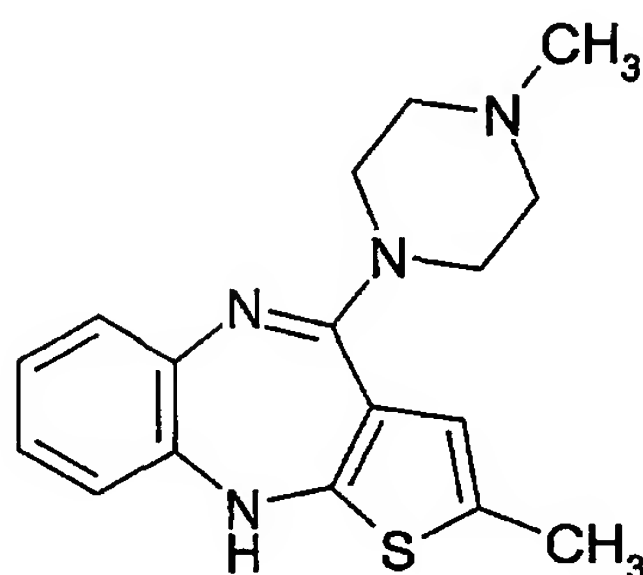
a) an X-ray powder diffraction obtained from a copper radiation source at ambient temperature containing 2-theta values at 8.1 ± 0.1 , 9.8 ± 0.1 , 13.6 ± 0.1 , 16.3 ± 0.1 , 21.6 ± 0.1 , and $22.1 \pm 0.1^\circ$; and

b) a solid-state ^{13}C nuclear magnetic resonance spectrum with peaks at the following chemical shifts 15.5, 43.6, 121.5, 123.2, 124.6, 127.3, 128.3, 130.3, 136.6, 148.8, and 162.4 ppm.

The reagents and materials for the present invention can be purchased or prepared by a variety of procedures well known to those of ordinary skill in the art. Olanzapine can be prepared by one of ordinary skill in the art, for example as described in U.S. Patent Nos. 5,229,382 and 5,736,541. In addition, olanzapine pamoate and olanzapine pamoate monohydrate can be prepared by one of ordinary skill in the art, for example as set forth in U.S. Patent No. 6,169,084 B1.

As used herein the term "substantially pure" refers to pure crystalline form of the compound comprising greater than about 90% of the desired crystalline form, and preferably greater than about 95% of the desired crystalline form.

It is understood by one of ordinary skill in the art that olanzapine has the following structure:



The examples set forth herein represent typical syntheses of the compounds of the present invention.

As used herein, the terms listed in the following table have the corresponding meanings as indicated:

Term	Meaning
¹ H NMR	Proton nuclear magnetic resonance spectroscopy
ss NMR	Solid state nuclear magnetic resonance spectroscopy
XRD	X-Ray Diffraction
XRPD	X-Ray Powder Diffraction
eq.	equivalents
g	grams
mg	milligrams
L	liters
mL	milliliters
μL	microliters
mol	moles
mmol	millimoles
m.p.	melting point
min	minutes
h or hr	hours
°C	degrees Celsius
aq.	aqueous
Celite®	diatomaceous earth filtering agent
RT or rt	room temperature
DMF	N,N-dimethylformamide
DMSO	methyl sulfoxide
EtOAc	ethyl acetate
THF	tetrahydrofuran
DME	1,2-dimethoxyethane
EtOH	ethanol
MeOH	methanol

Preparation 1

Preparation of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine pamoate (olanzapine pamoate, See for example Preparation 3
5 in U.S. Patent No. 6,169,084 B1).

Olanzapine (3.12 g, 0.01 mole) is dissolved in tetrahydrofuran (50 mL) with heating. Pamoic acid (3.88 g, 0.01 mole) is dissolved in tetrahydrofuran (100 mL) with heating. The two solutions are mixed and filtered through a pad of Celite® while it is still warm. The yellow solution is transferred to a Buchi flask and evaporated under reduced
10 pressure (bath temperature 50°C). After about 50 mL of solvent are removed ethanol (50 mL) is introduced and evaporation continued. A further 50 mL of ethanol is introduced after a further 50 mL of solvent is collected. Evaporation is continued until crystallization commences. The crystals are collected by filtration and dried under high vacuum at 120°C. m.p. 203-205°C.

15

Preparation 2

Preparation of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine pamoate (olanzapine pamoate monohydrate, See for example
Preparation 6 in U.S. Patent No. 6,169,084 B1).

20 Into a suitable beaker equipped with a magnetic stirrer is added methyl sulfoxide (22 ml), pamoic acid (2.49 g, 6.41 mmol), and olanzapine (2.0 g, 6.40 mmol). The slurry is stirred at 20-25°C to dissolve (about 20 minutes). The solution is added over 20 minutes to a 250 mL three-necked flask equipped with a mechanical stirrer and containing water (96 ml) at 40°C. After the addition is complete, the slurry is stirred
25 about 20 minutes at 40°C, cooled to 20-25°C over about 30 minutes, filtered, and washed with water (25 ml). The product is dried in vacuo at 50°C to provide the title compound (4.55g).

Example 1

Preparation of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine pamoate dihydrate (olanzapine pamoate dihydrate).

Olanzapine pamoate monohydrate (500 mg) is slurried in 1:1 v/v acetonitrile-H₂O (10 mL) for 6 days. After one day the color changes from bright yellow to pale yellow. The solids are isolated by vacuum filtration and washed with 1:1 v/v acetonitrile-H₂O to provide the title compound (465 mg).

Example 2

Additional preparation of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine pamoate dihydrate. (olanzapine pamoate dihydrate).

Olanzapine pamoate (10 g) is dissolved in 1:1 v/v methyl sulfoxide-acetonitrile (250 mL) and filtered. Water (300 mL) is then added dropwise, rapidly. The solid precipitate is allowed to resonate for about one hour, then isolated by vacuum filtration. The filter cake is washed with water (50 mL), followed by acetonitrile (50 mL), and is then air-dried for 30 minutes to provide the title compound (9.5 g).

Example 3

Additional preparation of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine pamoate dihydrate. (olanzapine pamoate dihydrate).

A wet ethyl acetate solution (400 mL) of olanzapine pamoate (20 g) is seeded with olanzapine dihydrate and slurried for 6 days. The solids are isolated by vacuum filtration, washed copiously with wet ethyl acetate and air dried to provide the title compound (20 g).

Comparative In Vitro Dissolution Test

In-vitro dissolution testing was performed to compare the olanzapine release rates for olanzapine pamoate monohydrate and the olanzapine pamoate dihydrate. The experimental conditions for the dissolution test are provided in Table 3.

Table 3. Summary of Experimental Conditions.

<u>Dissolution Parameter</u>	<u>Test Conditions</u>
Apparatus	USP Apparatus 2 (Paddle Apparatus)
Paddle Speed	50 RPM
Media	0.05% CTAB, pH 6.8 USP Buffer
Media Temperature	37°C
Media Volume	1000 mL
Sample Introduction	Weighed dry powder (approx. 172 mg partial dose)
Sampling Timepoints	0.25, 0.5, 0.75, 1, 2, 4, 6, 24 hours

A comparison of the data as provided in Table 4 demonstrates that, under the above
5 aqueous conditions, olanzapine pamoate dihydrate has a substantially lower release rate of
olanzapine than the olanzapine pamoate monohydrate.

Table 4. Olanzapine Release After 24 hrs. at 50 rpm Paddle Speed.

Compound	Average % Olanzapine Release (n=3)							
	0.25 hr.	0.5 hr.	0.75 hr.	1 hr.	2 hrs.	4 hrs	6hrs.	24 hrs.
Olanzapine Pamoate Monohydrate	27	39	46	52	62	73	77	83
Olanzapine Pamoate Dihydrate	19	26	30	33	40	45	47	59

10

Another dissolution experiment was performed in order to ensure that the media
conditions used to generate the profiles in Table 4 were not solubility limiting. This
experiment was performed using the same samples and media conditions but at a higher
paddle speed to provide the data listed in Table 5. These data show that the chosen media
15 conditions provided sufficient solubility for both the olanzapine pamoate dihydrate and
the olanzapine pamoate monohydrate.

Table 5. Olanzapine Release After 24 and 36 hrs. at 100 rpm Paddle Speed.

Compound	% Olanzapine Release (n=1)	
	24 hrs.	36 hrs.
Olanzapine Pamoate Monohydrate	99	99
Olanzapine Pamoate Dihydrate	95	97

5 Rabbit Assay

New Zealand White rabbits are selected for the evaluation of sustained release or depot formulations because the size of their leg muscles facilitates dose administration and evaluation of the injection site. Three rabbits of the same sex are used for each formulation with selection based on availability. The rabbits are at least 5 months old and weigh between 2.5 to 5 kg. Rabbits are given a single injection with a 20- or 21-gauge needle into the biceps femoris. The dose volume varies with the concentration of the formulation but does not exceed 2 mL per injection. The rabbits are given 10 mg of olanzapine/kg body weight.

A 2 mL blood sample is collected from the medial ear artery or jugular vein into heparinized collection tubes once prior to dose administration and at 4 hours after dose administration and again daily after 1, 2, 7, 10, and 14 days. Plasma is harvested and plasma concentration of olanzapine is determined by HPLC. Formulations of the instant invention can be tested in the rabbit assay.

20 Dog Assay

The beagle dog is selected because much is known about the pharmacokinetics of olanzapine in dogs. Since there is no difference in the pharmacokinetics of olanzapine between the sexes, dog selection is not based on sex. Three dogs (male or female) are used for each formulation. The dogs are adults (> 6 months old) and weighed between 8

to 21 kg. The dogs are given a single injection with a 20 or 21 gauge needle into the gluteal or biceps femoris muscle. The dose volume vary with the concentration of the formulation but does not exceed 2 mL per injection. The dogs are given 10 mg of olanzapine/kg of body weight.

5 At each time point, a 2 mL blood sample is collected from the jugular vein into heparanized collection tubes. Blood samples are collected once prior to dose administration and at various time points after dose administration throughout the 28-day period. Typical time points are at 0.5, 1, 2, 4, 8, and 24 hours after dose administration and once daily after 2, 4, 7, 14, 21, and 28 days. Plasma is harvested and plasma
10 concentration of olanzapine is determined by HPLC.

 In addition, the present invention provides a pharmaceutical composition, which comprises olanzapine pamoate dihydrate, and a pharmaceutically acceptable carrier, diluent, or excipient.

 The pharmaceutical compositions are prepared by known procedures using well-
15 known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient.
20 The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

 Some examples of suitable carriers, excipients, and diluents include lactose,
25 dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, micro-crystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents,
30 sweetening agents, or flavoring agents. Compositions of the invention may be formulated so as to provide sustained release of olanzapine pamoate dihydrate after administration to the patient by employing procedures well known in the art.

Preferably, the formulation has a prolonged sustained release of an effective amount of olanzapine after injection, such as intramuscular injection, for a period of greater than 7 days, more preferably at least 14 days, most preferably up to 30 days with a burst release of less than 15% active ingredient. The term "burst" is understood by those skilled in the art to mean the immediate release of active ingredient. In addition, a preferred formulation is injectable through a 21 gauge needle or smaller with an injection volume of 2 ml or less. Other desirable characteristics include the use of carriers or excipients that are toxicologically and pharmaceutically acceptable. For example, a certain amount of the olanzapine pamoate dihydrate is placed in a vial, which is then sterilized together with any additional contents and then sealed. Mixing with a suitable carrier just before use, may be provided with a complementary vial or other container containing the desired carrier. Water is an example of such a carrier. Formulations, including sustained release or depot formulations are desirable in unit dosage form suitable, preferably, for subcutaneous or intramuscular administration.

As used herein the term "patient" refers to a mammal, such as a mouse, guinea pig, rat, dog or human. It is understood that the preferred patient is a human.

As used herein, the terms "treating" or "to treat" each mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

As used herein the term "effective amount" refers to the amount or dose of the compound, upon single or multiple dose administration to the patient, which provides the desired effect in the patient under diagnosis or treatment.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose of compound administered, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication;

and other relevant circumstances. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, bucal or intranasal routes. Alternatively, the compound may be administered by continuous infusion.

- 5 Olanzapine is effective over a wide dosage range, the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages of from about 0.25 to 200 mg, preferably from 1 to 30 mg, and most preferably 1 to 20 mg per day may be used. In addition, a sustained release or depot
10 from several days to up to about one month.

WE CLAIM:

1. A compound which is olanzapine pamoate dihydrate.
2. A compound which is olanzapine pamoate dihydrate which is substantially pure.
- 5 3. A pharmaceutical composition comprising olanzapine pamoate dihydrate and a pharmaceutically acceptable carrier, diluent, or excipient.
4. A pharmaceutical composition according to claim 3 which is administered intramuscularly as a depot formulation.
5. A pharmaceutical composition according to claim 3 wherein the olanzapine
10 pamoate dihydrate is substantially pure.
6. A pharmaceutical composition according to claim 3 wherein the carrier is water.
7. A method of treating schizophrenia, acute mixed or manic episodes associated with bipolar I disorder, agitation associated with schizophrenia, agitation associated with
15 bipolar I disorder, agitation associated with dementia, or borderline personality disorder, comprising administering to a patient an effective amount of olanzapine pamoate dihydrate.

INTERNATIONAL SEARCH REPORT

International application No JS2005/046752

A. CLASSIFICATION OF SUBJECT MATTER C07D495/04 A61K31/5513 A61P25/18		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 169 084 B1 (BUNNELL CHARLES ARTHUR ET AL) 2 January 2001 (2001-01-02) cited in the application Paragraph 1, column 2. Preparation 6, columns 14-15. Claim 3.	1-3,7
A	WO 03/037903 A (DR. REDDY'S LABORATORIES LTD; CORD, JANET, I; REDDY, REGURI, BUCHI; RA) 8 May 2003 (2003-05-08) Claims 1-17	1-3,7
<div style="display: flex; justify-content: space-between;"> <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex. </div>		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents :</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search	Date of mailing of the international search report	
22 March 2006	06/04/2006	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Menchaca, R	

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US2005/046752

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
JP 2005-046752

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6169084	B1	02-01-2001	NONE
WO 03037903	A	08-05-2003	CA 2464306 A1 08-05-2003 EP 1440074 A1 28-07-2004